Q8 Pharmaceutical Development

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Table of Contents

1. Introduction

1.1 Objective of the Guideline

This guideline describes the suggested contents for the 3.2.P.2 Pharmaceutical Development section of a regulatory submission in the ICH M4 Common Technical Document (CTD) format.

The Pharmaceutical Development section provides an opportunity to present the knowledge gained through the application of scientific approaches, and risk management*, to the development of a product and its manufacturing process. It is first produced for the original marketing application and can be updated to support new knowledge gained over the lifecycle* of a product. The guideline also indicates areas where the provision of greater understanding of pharmaceutical and manufacturing sciences can create a basis for flexible regulatory approaches. The Pharmaceutical Development section is intended to provide a more comprehensive understanding of the product and manufacturing process for reviewers and inspectors.

1.2 Background

During the July 2003 ICH meeting in Brussels, agreement was reached on a common vision and approach for developing an international plan for a harmonized pharmaceutical quality system that would be applicable across the life cycle of a product. This plan emphasizes an integrated approach to review (assessment) and inspection based on scientific risk management. Several actions were outlined to implement this vision. An expert-working group (EWG) was established to develop guidance for pharmaceutical development, which will cover the lifecycle of a product.

1.3 Scope

This guideline is intended to provide guidance on the contents of Section 3.2.P.2 (Pharmaceutical Development) for drug products as defined in the scope of Module 3 of the Common Technical Document (ICH topic M4). The guideline does not apply to contents of submissions for drug products during the clinical research stages of drug development. However the principles in this guideline are important to consider during these stages. This guideline might also be appropriate for other types of products. To determine the applicability of this guideline for a particular type of product, applicants should consult with the appropriate regulatory authorities.

2. Pharmaceutical Development

The aim of pharmaceutical development is to design a quality* product and the manufacturing process to deliver the product in a reproducible manner. The information and knowledge gained from pharmaceutical development studies provide scientific understanding to support the establishing of specifications and manufacturing controls.

* See Glossary for definition

Information from pharmaceutical development studies is a basis for risk management. It is important to recognize that quality cannot be tested into products; i.e., quality should be built in by design. Changes in formulation and manufacturing processes during development should be looked upon as opportunities to gain additional knowledge and further support establishment of the design space*. Inclusion of knowledge gained from experiments giving negative results also can be useful in supporting the selected product and its manufacturing process.

The Pharmaceutical Development section should describe the knowledge that establishes that the type of dosage form selected and the formulation proposed are satisfactory for the purpose specified in the application. This section should include sufficient information in each part to provide an understanding of the development of the drug product and its manufacturing process. Summary tables and graphs are encouraged.

At a minimum, those aspects of drug substances, excipients, and manufacturing processes that are critical and that present a significant risk* to product quality, and therefore should be monitored or otherwise controlled, should be identified and discussed. These critical formulation attributes and process parameters are generally identified through an assessment of the extent to which their variation can have impact on the quality of the drug product.

In addition, the applicant can choose to conduct other pharmaceutical development studies that can lead to an enhanced knowledge of product performance over a wider range of material attributes, processing options and process parameters. Inclusion of this additional information in this section provides an opportunity to demonstrate a higher degree of understanding of manufacturing processes and process controls. This scientific understanding establishes the design space. In these situations, opportunities exist to develop more flexible regulatory approaches, for example, to facilitate:

- risk based regulatory decisions (reviews and inspections);
- manufacturing process improvements, within the approved design space described in the dossier, without further regulatory review;
- "real time" quality control, leading to a reduction of end-product release testing.

To realise this flexibility, the applicant should demonstrate an enhanced knowledge of product performance over a range of material attributes (e.g. particle size distribution, moisture content, flow properties), processing options and process parameters. This knowledge can be gained by, for example, application of formal experimental designs* or PAT*. Appropriate use of risk management principles can be helpful in prioritising the additional pharmaceutical development studies to collect such knowledge.

The design and conduct of the pharmaceutical development studies should be consistent with their intended scientific purpose and the stage of the development of the product. It

* See Glossary for definition

should be recognized that the level of knowledge gained, and not the volume of data, provides the basis for science-based submissions and their regulatory evaluation.

2.1 Components of the Drug Product

2.1.1 Drug Substance

The physicochemical and biological properties of the drug substance that can influence the performance of the drug product and its manufacturability, or were specifically designed into the drug substance (e.g., crystal engineering), should be identified and discussed. Examples of physicochemical and biological properties that might need to be examined include solubility, water content, particle size, crystal properties, biological activity, and permeability. These properties could be inter-related and might need to be considered in combination. Some of these properties can change with time and might be supplier dependent.

To evaluate the potential effect of drug substance physicochemical properties on the performance of the drug product, studies on drug product might be warranted. For example, the ICH *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* describes some of the circumstances in which drug product studies are recommended (e.g., Decision Tree #3 and #4 (Part 2)). The knowledge gained from the studies investigating the potential effect of drug substance properties on drug product performance can be used, as appropriate, to justify elements of the drug substance specification (3.2.S.4.5).

The compatibility of the drug substance with excipients listed in 3.2.P.1 should be discussed. For products that contain more than one drug substance, the compatibility of the drug substances with each other should also be discussed.

2.1.2 Excipients

The excipients chosen, their concentration, and the characteristics that can influence the drug product performance (e.g., stability, bioavailability) or manufacturability should be discussed relative to the respective function of each excipient. Compatibility of excipients with other excipients, where relevant (for example combination of preservatives in a dual preservative system), should be established. The ability of excipients (e.g., antioxidants, penetration enhancers, disintegrants, release controlling agents) to provide their intended functionality, and to perform throughout the intended drug product shelf life, should also be demonstrated. The information on excipient performance can be used, as appropriate, to justify the choice and quality attributes of the excipient, and to support the justification of the drug product specification (3.2.P.5.6).

Information to support the safety of excipients, when appropriate, should be cross-referenced (3.2.P.4.6).

2.2 Drug Product

2.2.1 Formulation Development

A summary should be provided describing the development of the formulation, including identification of those attributes that are critical to the quality of the drug product, taking into consideration intended usage and route of administration.

The summary should highlight the evolution of the formulation design from initial concept up to the final design. This summary should also take into consideration the choice of drug product components, (e.g. the properties of the drug substance, excipients, container closure system, any relevant dosing device) the manufacturing process, and, if appropriate, experiences gained from the development of similar drug product(s).

Information from formal experimental designs can be useful in identifying critical or interacting variables that might be important to ensure the quality of the drug product. Any excipient ranges included in the batch formula (3.2.P.3.2) should be justified in this section of the application: this justification can often be based on the experience gained during the development of the formulation and manufacturing process.

A summary of all formulations used in clinical safety and efficacy, bioavailability, or bioequivalence studies should be provided. Any changes between the proposed commercial formulation and those formulations used in pivotal clinical batches and primary stability batches should be clearly described and the rationale for the changes provided.

Information from comparative in vitro studies (e.g., dissolution), or comparative in vivo studies (e.g., bioequivalence), that links clinical formulations to the proposed commercial formulation described in 3.2.P.1 should be summarized and a cross-reference to the studies (with study numbers) should be provided. Where attempts have been made to establish an in vitro/in vivo correlation the results of those studies, and a cross-reference to the studies (with study numbers), should be provided in this section. A successful correlation can assist in the selection of appropriate dissolution acceptance criteria, and can potentially reduce the need for further bioequivalence studies following changes to the product or its manufacturing process.

Any special design features of the drug product (e.g., tablet score line, overfill, anti-counterfeiting measure) should be identified and a rationale provided for their use. Information to support the appropriateness of such features should be provided.

2.2.2 Overages

The use of overages of drug substance(s) in drug products is discouraged.

An overage is a fixed amount of the drug substance added to the formulation in excess of the label claim. Any overages in the manufacture of the drug product, whether they appear in the final formulated product or not, should be justified considering the safety and efficacy of the product. Information should be provided on the 1) amount of overage, 2) reason for the overage, (e.g., to compensate for expected and documented manufacturing losses), and 3) justification for the amount of overage. The overage should be included in the amount of drug substance listed in the representative batch formula (3.2.P.3.2).

2.2.3 Physicochemical and Biological Properties

The physicochemical and biological properties relevant to the performance or manufacturability of the drug product should be identified and discussed. These could include formulation attributes such as pH, osmolarity, ionic strength, lipophilicity, dissolution, redispersion, reconstitution, particle size distribution, particle shape, aggregation, polymorphism, rheological properties, globule size of emulsions, biological activity or potency, and/or immunological activity. Physiological implications of formulation attributes such as pH should also be addressed. The discussion should cross-reference any relevant stability data in 3.2.P.8.3.

A summary of the development studies that were carried out to investigate the potential impacts of the physicochemical and biological properties of the drug product and the appropriateness of the drug product acceptance criteria should be reported in this section of the application (3.2.P.2.2.3). These studies could include, for example, the development of a dissolution or drug release test, or the development of a test for respirable fraction of an inhaled product, where appropriate. Physiological implications of drug substance and formulation attributes should be addressed. For example, information could be provided from studies to investigate whether acceptance criteria for polymorphism should be included in the drug product specification. Similarly, information to support the robustness of the formulation and manufacturing process with respect to the selection of dissolution versus disintegration testing, or other means to assure drug release, could be provided in this section. See also ICH *Q6A Specifications: Test Procedures And Acceptance Criteria For New Drug Substances And New Drug Products: Chemical Substances*; Decision Tree #4 (Part 3) and Decision Tree #7 (Part 1).

2.3 Manufacturing Process Development

The selection, the control, and any optimisation of the manufacturing process described in 3.2.P.3.3 (i.e., intended for commercial production batches) should be explained. It is important to consider the critical formulation attributes, together with the available manufacturing process options (e.g., dry granulation vs. wet granulation, terminal sterilisation vs. aseptic processing), in order to address the selection of the manufacturing process and confirm the appropriateness of the components (i.e., excipients). Appropriateness of the equipment used for the intended products should be discussed. Process development studies should provide the basis for process optimisation, process validation and process control requirements. Where appropriate, such studies should

address microbiological as well as physical and chemical attributes. The knowledge gained from process development studies can be used, as appropriate, to justify the drug product specification (3.2.P.5.6). An assessment of the ability of the process to reliably produce a product of the intended quality (e.g., the performance of the manufacturing process under different operating conditions, at different scales, or with different equipment) should be provided.

The manufacturing process development programme should identify the critical process parameters that should be monitored or controlled (e.g., granulation end point) to ensure that the product is of the desired quality.

For those products intended to be sterile an appropriate method of sterilization for the drug product and primary packaging material should be chosen and the choice justified.

Significant differences between the manufacturing processes used to produce the clinical safety and efficacy, bioavailability, bioequivalence, or primary stability batches and the process described in 3.2.P.3.3 should be discussed. The discussion should summarise the influence of the differences on the performance and manufacturability of the product. The information should be presented in a way that facilitates comparison of the processes and the corresponding batch analyses information (3.2.P.5.4). The information should include, for example, (1) the identity (e.g., batch number) and use of the batches produced using the specified equipment (e.g., bioequivalence study batch number), (2) the manufacturing site, (3) the batch size, and (4) any significant equipment differences (e.g., different design, operating principle, size).

In order to provide flexibility for future process optimisation, when describing the development of the manufacturing process, it is useful to describe any measurement systems that allow monitoring of critical attributes or process end-points. Collection of process monitoring data during the development of the manufacturing process can provide useful information to enhance process understanding. The process controls that provide process adjustment capabilities to ensure control of all critical attributes should be described. These provide a means for a risk control strategy.

An assessment of process robustness can be useful in risk assessment and risk reduction[*], to support future manufacturing and process optimisation, especially in conjunction with the use of structured risk management tools.

2.4 Container Closure System

The choice and rationale for selection of the container closure system(s) for the commercial product(s) (described in 3.2.P.7) should be discussed. Consideration should be given to the intended use of the drug product and the suitability of the container closure system for storage and transportation (shipping), including the storage and shipping container for bulk drug product, where appropriate.

[*] See Glossary for definition

The choice of materials for primary packaging should be justified. The discussion should describe studies performed to demonstrate the integrity of the container and closure. A possible interaction between product and container(s) or label should be considered. This applies also to admixture or dilution of products prior to administration e.g. product added to large volume infusion containers.

The choice of primary packaging materials should consider, e.g., choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching), and safety of materials of construction.

If a dosing device is used (e.g., dropper pipette, pen injection device), it is important to demonstrate that a reproducible and accurate dose of the product is delivered under testing conditions which, as far as possible, simulate the use of the product.

2.5 Microbiological Attributes

Where appropriate, the microbiological attributes of the drug product should be discussed in this section (3.2.P.2.5). The discussion should include, for example:

- The rationale for performing or not performing microbial limits testing for nonsterile drug products, (e.g., Decision Tree #8 in ICH Q6A *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances)*

- The selection and effectiveness of preservative systems in products containing antimicrobial preservative or the antimicrobial effectiveness of products that are inherently antimicrobial

- For sterile products, the integrity of the container closure system as it relates to preventing microbial contamination.

Although chemical testing for preservative content is the attribute normally included in the drug product specification, antimicrobial preservative effectiveness should be demonstrated during development. The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling microorganisms by using an antimicrobial preservative effectiveness test.

2.6 Compatibility

The compatibility of the drug product with reconstitution diluent(s) or dosage devices (e.g., precipitation of drug substance in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labelling. This information should cover the recommended in-use shelf life, at the recommended storage temperature and at the likely extremes of concentration. Where the label recommends dilution or mixing of solid dose forms (for example with drinks) prior to

administration, appropriate compatibility studies should be described.

3. Glossary

Design Space: the design space is the established range of process parameters that has been demonstrated to provide assurance of quality. In some cases design space can also be applicable to formulation attributes. Working within the design space is not generally considered as a change of the approved ranges for process parameters and formulation attributes. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process.

Formal Experimental Design: a structured, organized method for determining the relationship between factors (Xs) affecting a process and the output of that process (Y). Also known as "Design of Experiments".

Lifecycle: all phases in the life of a product from the initial development through pre- and post-approval until the product's discontinuation.

PAT: Process Analytical Technologies - a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of assuring final product quality.

Quality: degree to which a set of inherent properties of a product, system or process fulfils requirements

Risk: the combination of the probability of occurrence of harm and the severity of that harm (from ISO/IEC Guide 51)

Risk Management: systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling and communicating risk.

Risk Reduction: actions taken to lessen the probability of occurrence of harm and the severity of that harm